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Attorney Docket No. 44033-122 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of :

Marc J. MCKENNON, et al. :

Application No.: 09/859,503 : Group Art Unit: 1624

Filed: May 18, 2001 : Examiner: M. Berch

For: PYRIDOPYRIMIDINE COMPOUNDS AND THEIR USES

TRANSMITTAL OF APPEAL BRIEF

Honorable Commissioner for Patents
Mail Stop Appeal Brief-Patents

Sir:

Submitted herewith in triplicate is Appellant(s) Appeal Brief in support of the Notice of Appeal filed December 9, 2002. Please grant a four (4) month extension of time. Please charge the Appeal Brief and Extension of Time fees (**small entity**) to Deposit Account 500417.

To the extent necessary, please grant any further extension of time under 37 C.F.R. 1.136 deemed necessary. Please charge any shortage in fees due, or any excess fees paid, to Deposit Account 500417.

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Respectfully submitted,

Date: June 9, 2003

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APPEAL BRIEF

Honorable Commissioner for Patents
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Sir:

Appellants herein appeal from the Examiner's rejection of claims. The claims have been twice rejected. Appeal is timely and proper pursuant to 37 CFR § 1.191(a). This Appeal Brief is submitted in support of the Notice of Appeal filed December 9, 2002.

REAL PARTY IN INTEREST

This application is assigned to Cell Therapeutics, Inc. by assignment recorded on August 20, 2001, at Reel 012193, Frame 0444.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 1, 2 and 4-37 are pending herein. Claim 3 has been canceled. No claims have been indicated as being allowable. A copy of claims 1, 2 and 4-37 on appeal, as rejected in the Office Action dated November 5, 2002 (Paper No. 12) from which the appeal was taken, are found in the APPENDIX A attached hereto.[1]

STATUS OF AMENDMENTS

All amendments filed in this case before January 9, 2002, have been entered. An amendment is being filed with this Appeal Brief to amend claims 1, 2 and 7 to overcome grounds of rejection under 35 U.S.C. § 112, second paragraph, set forth in paragraphs 1 and 4 in the Office Action (Paper No. 12) from which this appeal was taken.

SUMMARY OF INVENTION

The invention is directed to a therapeutic compound, a pharmaceutical composition containing said compound, methods of using the same, and a method for treating a cell-mediated inflammatory response in mammals. In particular, the compounds and/or compositions inhibit the activity mediated by a cytokine by suppressing the signaling activity.

The therapeutic compound of the invention comprises one of the following formulae:

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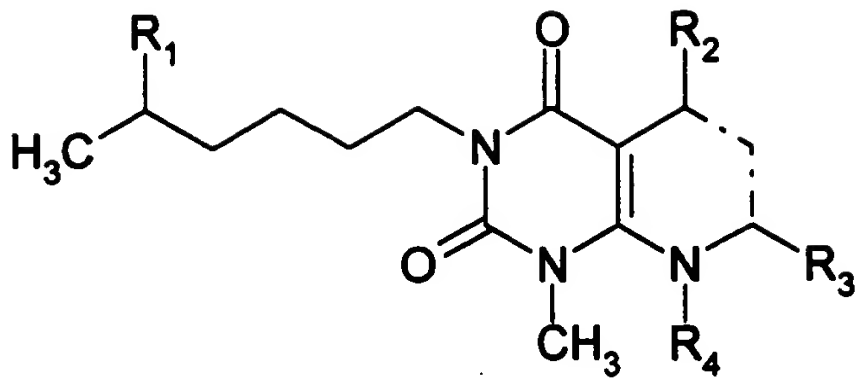
[1]The Office Action also included an objection to claims 4-7 under 37 CFR § 1.75(c) as being improper dependent claims because they fail to further limit the subject matter of a previous claim. Because Appellants are aware that the objection is not reviewable by the Board of Patent Appeals and Interferences, a petition for supervisory review of the objection was filed on January 6, 2003. As a result, in Paper 16, dated March 5, 2003, the Examiner was reversed and the objection was withdrawn.



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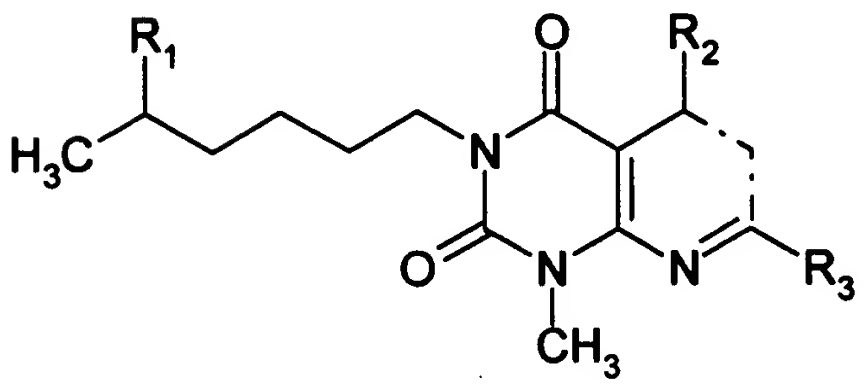

wherein:

R_1 is selected from a member of the group consisting of hydrogen, hydroxyl, methoxyl, acylamino group, cyano group, sulfo, sulfinyl, sulfhydryl (mercapto), sulfeno, sulfanilyl, sulfamyl, sulfamino, and phosphino, phosphinyl, phospho, phosphono and $-NR_aR_b$, wherein each of R_a and R_b may be the same or different and each is selected from the group consisting of hydrogen and optionally substituted: $C_{(1-20)}$alkyl, $C_{(3-12)}$cycloalkyl, $C_{(2-20)}$alkenyl, $C_{(3-12)}$cyclo-alkenyl, $C_{(2-20)}$alkynyl, aryl, heteroaryl, and heterocyclic group;

R_2 and R_3 are independently selected from a member of the group consisting of halo, oxo, $C_{(1-20)}$alkyl, $C_{(1-20)}$hydroxyalkyl, $C_{(1-20)}$thioalkyl, $C_{(1-20)}$alkylthio, $C_{(1-20)}$alkylaminoalkyl, $C_{(1-20)}$aminoalkyl, $C_{(1-20)}$aminoalkoxyalkenyl, $C_{(1-20)}$aminoalkoxyalkynyl, $C_{(1-20)}$diaminoalkyl, $C_{(1-20)}$triaminoalkyl, $C_{(1-20)}$tetraaminoalkyl, $C_{(1-20)}$alkylamido, $C_{(1-20)}$alkylamidoalkyl, $C_{(1-20)}$amido-alkyl, $C_{(1-20)}$acetamidoalkyl, $C_{(2-20)}$alkenyl, $C_{(2-20)}$alkynyl, $C_{(1-20)}$alkoxyl, $C_{(1-20)}$alkoxyalkyl, $C_{(1-20)}$dialkoxyalkyl, and $-NR_aR_b$; and

R_4 may be hydrogen or an optionally substituted member of the group consisting of $C_{(1-20)}$alkyl, $C_{(3-12)}$cycloalkyl, $C_{(2-20)}$alkenyl, $C_{(3-12)}$cycloalkenyl, $C_{(2-20)}$alkynyl, aryl, heteroaryl, and heterocyclic group.

The compounds of the invention include resolved enantiomers, diastereomers, tautomers, salts and solvates thereof. The invention further provides a method for inhibiting activity in a cell mediated by a cytokine comprising the steps of (i) contacting cells mediated by the cytokine with the therapeutic compound and then determining that the activity initiated by the cytokine in the cell is inhibited.

ISSUES

1. Claims 1, 2, 4-7 and 18-37 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, on four grounds. The issues presented by this rejection are as follows:

(a) Whether a person skilled in the art would have been reasonably apprised of the scope of claim 19 with respect to with respect to the use of the term "determining."

(b) Whether a person skilled in the art would have been reasonably apprised of the scope of claim 19 with respect to with respect to the use of the term "cellular process or activity."

(c) Whether a person having ordinary skill in the art would have been reasonably

apprised of the scope of claims 23 and 24.

(d) Whether a person having ordinary skill in the art would have been reasonably apprised of the scope of claims 1, 2, 4-7 and 18-37 with respect to the meaning of "thioalkyl"

2. Claims 1, 2 and 18-37 stand rejected under 35 U.S.C. § 112, first paragraph. The issue is whether the specification as filed contains subject matter which would have reasonably conveyed to a person skilled in the relevant art that the inventors, at the time the application was filed, had possession of the invention recited in claims 1, 2 and 18-37.

3. Claims 10, 11, 14, 15 and 17 stand rejected under 35 U.S.C. § 112, first paragraph. The issue is whether the specification is enabling for each of the compounds recited in claims 10, 11, 14, 15 and 17.

4. Claims 1-36 stand rejected under 35 U.S.C. § 112, first paragraph. The issue is whether the specification is enabling for preparing solvates of the compounds recited in claim 1.

5. Claims 19-25 stand rejected under 35 U.S.C. § 112, first paragraph. The issue is whether undue experimentation would be required for a person having ordinary skill in the art to make and use the claimed invention.

GROUPING OF CLAIMS

Under 35 U.S.C. § 282, Appellants submit that the patentability of any one appealed claim is not solely predicated on the patentability of the remaining appealed claims. Each claim of this patent application is separately patentable and upon issuance of a patent will be entitled to a separate presumption of validity. Pursuant to 37 C.F.R. § 1.192(5), each of the pending claims will separately stand or fall in this appeal.

THE ARGUMENT

Claims 1, 2 and 4-37 on appeal have been rejected under 35 U.S.C. § 112, first and second paragraphs, on numerous grounds. Appellants arguments with respect to each rejection is set forth below.

REJECTION OF UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2, 4-7 and 18-37 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the following grounds:

1. The Examiner asserts that the second step in claim 19 is inconsistent with the preamble. The preamble speaks in terms of "inhibiting" activity while step 2 is directed to "determining" that the activity is inhibited. The Examiner alleges that the term "determining" is indefinite because he does not know if it means "measuring the inhibition after it has occurred" or whether it is "just the mental step of observing that the inhibition after it has occurred." The Examiner considers the preamble to be directed to a "physical act" while the term "determining" is a "purely mental act."

Appellants respectfully submit that a person having skill in the art would readily understand the scope of the rejected claim. The Examiner acknowledges in his rejection of the claim under 35 U.S.C. § 112, first paragraph, that the "scope of the claim is clear: it covers any activity mediated by any cytokine" (paragraph bridging pages 13 and 14 of the Office Action (Paper No. 12)). The preamble states a "method for inhibiting an activity mediated by a cytokine." Thus, the method is directed to inhibiting cytokine activity. The first step in the method is to contact cytokine responsive cells with a compound recited in claim 1. This step is clear. A person having ordinary skill in the art would have understood this step to mean that the cytokine responsive cells are cells being mediated by the cytokine and that these cells are

contacted by the therapeutic compound recited in claim 1. The second step in the method is to determine that the cellular process or activity of the cell is inhibited. According to the Examiner, "most cellular activities are mediated by cytokines" (see the paragraph bridging pages 13 and 14 of the Office Action (Paper No. 12)). See also the definition of cytokines on page 452 of Steadman's Medical Dictionary and in the Dictionary of *Microbiology and Molecular Biology*, 3rd Edition. Copies of both definitions are attached in APPENDIX B.

The term "determining" is not defined in the specification. Accordingly, the term is to be interpreted in accordance with its ordinary and customary meaning . *In re Bass*, 65 USPQ2d 1156, (Fed. Cir. 2002); *Lantech, Inc. v. Keip Mach. Co.*, 32 F.3d 542, 547, 31 USPQ2d 1666, 1670 (Fed. Cir. 1994) ("[w]ords in a claim are to be given their ordinary and accustomed meaning unless the inventor chose to be his own lexicographer in the specification"). On page 346, of *Webster's Ninth New Collegiate Dictionary (1989)*, the word "determine" is defined as meaning "to come to a conclusion." A copy of page 346 is attached as Exhibit C to Appellants' response filed September 30, 2002. Therefore, a person having ordinary skill in the art would have understood "determining that the cellular process or activity mediated by the cytokine is inhibited" to come to a conclusion that after the cytokine responsive cells are contacted with the compound of claim 1, the cellular process or activity mediated by the cytokine is inhibited by the compound recited in claim 1.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

2. The Examiner made a finding that the phrase "cellular process or activity" in claim 19 is unclear because he saw no difference between "process" and "activity." While these terms are not defined in the specification, they are to be interpreted in accordance with their

ordinary meanings. *See In re Bass* and *Lantech, Inc. v. Keip Mach. C., supra*. Their ordinary meanings are different. As a noun, "process" means "something going on." The term "activity" on the other hand means "a state of being active" or a state of being characterized by action rather than by contemplation or speculation. Copies of the dictionary definitions of these terms were attached as Exhibit D to Appellants' response filed September 30, 2002. As evidenced by their definiations, the terms are not equivalent in scope as asserted by the Examiner.

The Examiner contends that this argument is "not understood." According to the Examiner:

> In terms of a cell, something going on, and being active, mean exactly the same thing. If a cell is active, it means that something is going on. If something is going on in the cell, that means that it is active. In other words, activity in a cell means that a cellular process is going on.

It is established law that a patent applicant is entitled to be his or her own lexicographer so long as terms are clearly defined and not given meanings repugnant or abhorrent to the ordinary meaning. *In re Barr*, 444 F.2d 588, 170 USPQ 330 (1971). The meanings for "process" and "activity" set forth above are not repugnant or abhorrent to their ordinary meanings. There is no issue that the scope of the claim is unclear, only the Examiner's personal opinion that the terms mean the same thing. The Examiner's opinion is not the standard for determining indefiniteness.

The Examiner does not assert that claim 19 is indefinite because it does not set out and circumscribe the claimed invention with a *reasonable* degree of precision and particularity. *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). The claims must be read, not in a vacuum, but in light of the prior art and the disclosure, as one of ordinary skill in the art. *Id.* In order to satisfy the requirements of the second paragraph of 35 U.S.C. § 112, a claim must accurately define the invention in the technical sense. *See In re Knowlton*, 481 F.2d 1357, 1366, l'8 USPQ 486, 492-3 (CCPA 1973). The test is whether a person having ordinary skill in the art

reading the claim would have understood the scope of the claim. According to the Examiner in his rejection of the claim under 35 U.S.C. § 112, first paragraph, *infra*, the "scope of the claim is clear ..." (see the paragraph bridging pages 13 and 14 of the Office Action (Paper No. 12)). The Examiner has not presented any evidence that would have lead a person having ordinary skill in the art to reasonably conclude that the claim is indefinite because the term "process and activity" is not understood.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

3. The Examiner asserts that the scope of claims 23 and 24 is unclear. Claims 23 and 24, respectfully, recite that the "activity" of the method defined by claim 19 is "the secretion of proinflammatory cytokines" and "the secretion of antiinflammatory cytokines." The Examiner's rejection to the claims appears to be based on undue breadth on the ground that undue experimentation would be required to identify the cytokines which are inflammatory from those which are not inflammatory. The rejection does not appear to be based on the preciseness or indefiniteness of language in the claims. It is well established law that that breadth is not indefiniteness. *In re Gardner,* 427 F.2d 786, 788, 166 USPQ 138, 140 (CCPA 1970); *In re Conley*, 490 F.2d 972, 975, 180 USPQ 454, 456 (CCPA 1974). If the Examiner is arguing that the claims are unduly broad based on a non-enabling disclosure, then the rejection would be under 35 U.S.C. § 112, first paragraph, and not the second paragraph of 35 U.S.C. § 112. Assuming arguendo that the rejection is a proper rejection under 35 U.S.C. § 112, the Examiner has not presented any evidence to support his conclusions that the "determination of the properties of a cytokine is a major undertaking, and for the great majority, virtually nothing is known" and that "[d]determining that a given cytokine does <u>not</u> fall into claim 23 or claim 24

would take extensive research, especially into [sic] the cytokine happened to fall into neither category" (underscoring in the original; page 4, ¶ 5). The finding of undue experimentation by the Examiner is based on a mere conclusion and is not supported by any evidence of record in this patent application. *In re Thrift*, 298 F.3d 1357, 63 USPQ2d 2002, (Fed. Cir. 2002). Reliance on common knowledge does not fulfill the Examiner's obligation to cite references in support of his or her conclusion. *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002).

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

4. The Examiner objected to the term "thioalkyl" as not being standard nomenclature. Contrary to the position taken by the Examiner, the term is standard nomenclature and has been used in issued patents. See U.S. Patent No. 5,849,780 at col. 18, line 37 and claim 15, col. 99, line 27. A copy of the pertinent portions of the patent are attached in APPENDIX C. During prosecution, Appellants cited claim 15 in issued patent, U.S. Patent No. 5,849,780, wherein R_9 is defined as a "C_1-C_7-thioalkyl" as an example. The Examiner did not comment on the use of the term in the aforementioned patent, but rationalized his rejection as follows:

> Thio as a generic prefix simply indicating the presence of sulfur. It is of course possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could even possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. CH_3-S-CH_2- or possibly the sulfur could be a double bonded substituent rather than a single bonded one, e.g. CH_3-C(=S)-CH_2-[sic, .] This specification gives no clear evidence as to which of these plausible choices was originally intended, as the extensive list of definitions does not cover this. The traverse is unpersuasive. Applicants state "it is an alkyl containing a sulfur atom." That is impossible. An alkyl cannot contain a S atom. Alkyl is a group of the formula $-C_nH_{2n+1}$, as is set forth in any dictionary, and thus does not contain a Sulfur. Alkyl might be connected via a S atom, it might be substituted by =S or by —SH, etc, but alkyl itself does not contain S.

The term "thio" is defined in *Hawley's Condensed Chemical Dictionary* as being a "prefix used

in chemical nomenclature to indicate the presence of sulfur in a compound, usually a substitute for oxygen." In the same *Dictionary*, "alkyl" is defined as "a paraffinic hydrocarbon group which may be derived from an alkane by dropping one hydrogen from the formula." A copies of the definitions are attached in APPENDIX D.

In view of the forgoing definitions, a "thioalkyl" would be an alkyl group which contains a thio group as a substituent, and not a replacement for a carbon atom. An example of such a group is HS–CH_2–CH_2–. The nomenclature would be similar to a hydroxyalkyl group, except that a sulfur atom is substituted for oxygen. For the foregoing reasons, the meaning of the term "thioalkyl" would have been understood by a person having ordinary skill in the art.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

REJECTION OF CLAIMS 1, 2, 4-7 AND 18-37 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1, 2 and 18-37 stand rejected under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, p.5, lines 7-10). The Examiner bases the rejection on the ground that "[T]he third structural formula in claim 1 lacks description in the specification" (Office Action, p. 5, lines 11). In an interview held with the Examiner on July 26, 2002, the Examiner told the undersigned that he meant the second appearing structural formula in the claim because only two structural formulae appear in claims 1 and 37. Assuming arguendo that the Examiner meant the second appearing formula, he rationalized his rejection as follows:

The third [sic, second] structural formula in claim 1 … is a generic formula where

> R_4 is absent. No such formula exists in the specification, nor does the definition of R_4 include that option. Although there are a few such species present, that does not provide description for the genus itself, only the species themselves. The traverse is unpersuasive. One of ordinary skill in the art is not going to have "recognized" that a structure that clearly depicts R4 is present actually has R4 as absent. The R4, and the bond to the R4 are not depicted as optional. Therefore, one of ordinary skill in the art would understand that the in that structure, the option of there being a double bond to the N cannot exist for that bond, although it can exist for other bonds in the ring. The additional species that applicants point to simply do not fall within the genus. [Underscoring in the original.]

Claim 1 was amended to overcome the Examiner's objection to the original structural formula because the Examiner found the structural formula could include a tetravalent nitrogen. The original formula included dashed lines which were defined to represent single or double bonds. A person having ordinary skill in the art reading the original structural formula and knowing that nitrogen is a trivalent atom would have recognized that one structure would be represented by —N(R_4)— and that another structure would be —N to satisfy the trivalent property of the N atom. Such a person would have also necessarily recognized that with the latter structure, R_4 would not have been present. For example, this is evident by the disclosure of structural formulas in claims 8 and 10. It is not necessary that Applicants disclose all species represented by the second formula in claim 1 since there are a sufficient number of species disclosed that would have enabled a person having ordinary skill in the art to understand the scope of the claims. For example, see claims 10, 11, 14, 15 and 17 and see pages 35-37 and the Examples in the specification for support for the structural formula. While Appellants are of the opinion that the original formula is not indefinite and that a person skilled in the art would have understood the scope of the claim, in order to appease the Examiner and to advance prosecution, the original formula was split into to separate formulas to show that a tetravalent nitrogen was not intended. The splitting of the original formula does not represent new matter, but an alternate way of illustrating by structural formulas the compounds within the scope of the original

structural formula. On reading the specification, a person having ordinary skill in the art would have recognized that the original formula could be split into two separate formulas as set forth in the claims to accommodate the objection by the Examiner as to the valance of nitrogen.

The Examiner made a finding that a person skilled in the art "is not going to have 'recognized' that a structure that clearly depicts R4 is present actually has R4 as being absent" and that "R4 and the bond to the R4 are not depicted as optional" (underscoring in the original). Appellants disagree with this finding. The original formula included the option to include, or not to include, R4. This is clearly demonstrated by the original formula and the Examples at pages 8 and 32 of the specification and by the preferred structures illustrated on pages 35 and 36 and including the Examples 1-10 on pages 47-59 of the specification. A person having ordinary skill in the art reading of the specification would have reasonably understood at the time of filing of the application that the general formula intended to cover the disclosed preferred compounds and the compounds prepared in accordance with the Examples.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

REJECTION OF CLAIMS 10, 11, 14, 15 AND 17 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 10, 11, 14, 15 and 17 stand rejected under 35 U.S.C. § 112, first paragraph, because "the specification while being enabling for one isomer, does not reasonably provide enablement for the other isomer" (Office Action, p. 5, line 23 to p. 6, line 1). According to the Examiner, this issue is that the compounds recited in claims 10, 11, 14, 15 and 17 "have not ascribed utility, since the utility is tied to a formula which requires that R4 be present" (Office Action, p. 6, lines 9-10). The specification discloses how to make the compound recited in claim 14. The details of the synthesis is described in Example 7 on pages 56-57 of the specification. In

addition, Table 1 on page 60 of the specification summarizes the effect of the compound recited in claim 14 on IL-12 signaling. See Example 11 on page 59 of the specification. Therefore, contrary to the Examiner's finding, claim 14 has disclosed utility.

In addition, the specification discloses in detail how to make the compounds recited in claims 10, 11, 15 and 17. See Examples 3, 4, 8 and 10 on pages 50, 51 and 55-59 of the specification. In Example 12 on pages 61-62 of the specification, the compounds of claims 3. 4, 8 and 10, *inter alia*, were tested in a modified acute assay to screen for compounds that perturb IL-12 signaling. Therefore, each of these compounds has a disclosed utility. See Table 3 on pages 62-63 of the specification.

The application satisfies the requirement of 35 U.S.C. § 101 by disclosing utility for the invention. On pages 35-37 of the specification, the preferred compounds are disclosed. These compounds which include, *inter alia*, the compounds recited in claims 10, 11, 14, 15 and 17. Page 35, lines 9-16 of the specification refers to the compounds as regulating cytokine activity. In particular, the disclosure states:

> In addition to their structural characteristics, the novel pyridopyrimidine-based compounds of the invention can regulate the aberrant or altered express of one or more cytokines that occurs in various condition, including, for example, pathologies, immune responses and inflammatory responses, which are characterized, in part, by aberrant or altered cytokine activity and, therefore, are amendable to regulation by one or more cytokine regulatory agents. A skilled artisan or scientist using routine protocols or assays, such as the assays disclosed in the Examples below or in the literature, may readily confirm the utility of the compounds disclosed herein.

The specification further includes an extensive discussion on methods of use at pages 37-40 and an extensive discussion on the pharmaceutical compositions and dosage at pages 40-46. This disclosure as well as the detailed synthesis provided in Examples 3, 4, 7, 8 and 10 of the specification would have provided sufficient guidance to a person having ordinary skill in the art

as to how to make and use the compounds recited in claims 10, 11, 14, 15 and 17.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

REJECTION OF CLAIMS 1-36 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-36 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for solvates" (Office Action, p.6, lines 14-15). It is Appellants position that solvates of the claimed compounds could be made using know techniques in the art. According to the Examiner:

> One skilled in the art knows that solvates are prepared by exposing the compound to solvent (e.g., by preparing in the presence of solvent) and then isolating the solid. If the compound inherently forms solvates, then one will get a solvate; if not, one will not. That is, some compounds form solvates; some do not. These compounds, judging by the evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound which does not naturally form one, to form a solvate. The specification does not even seem to be aware of the problem. [Office Action, p. 7, lines 8-15.]

While conceding that a person having ordinary skill in the art would know how to make a solvate, the Examiner finds that "judging by the evidence of the specification," solvates of the compounds could not be formed. The Examiner further contends that one cannot "force a compound which does not naturally [form a solvate] ... to form a solvate" (Office Action, p. 7, lines 13-14). These statements represent conclusions, and are not factual findings based on evidence.

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation. *United States V. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529

F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). In determining whether a disclosure would require undue experimentation to make the claimed subject matter, the Examiner must consider the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988), citing with approval *Ex parte Forman*, 230 USPQ 526, 547 (Bd. Pat. App. & Int. 1986). The burden is on the Examiner to establish a reasonable basis to question the adequacy of Applicants' disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 370 (CCPA 1971).

The Examiner's rejection appears to be based on a finding that no working examples are presented in the specification for making solvates of the claimed compounds, and that to make a solvate of the claimed inventive compounds would require undue experimentation. A solvate is a "nonaqueous solution or dispersion in which there is a noncovalent or easily reversible combination between solvent and solute, or dispersion means or disperse phase."[2] The Examiner admits that "[o]ne skilled in the art knows that solvates are prepared by exposing the compound to solvent (e.g., by preparing in the presence of solvent) and then isolating the solid" (Office Action, p. 7, lines 8-10). He makes the statement that "judging by the evidence of the specification," the compounds of the claimed invention would not form a solvate and that the "specification teaches no methods for overcoming this deficiency, i.e. to force a compound,

[2] *Stedmans's Medical Dictionary*, 27th Edition, Lippincottt Williams & Wilkins, Philadelphoa, Penn., p. 1654

which does not naturally form one, to form a solvate" (Office Action, p. 5, lines 12-14). The Examiner has not explained the basis as to why the compounds of the invention would not form solvates. The Examiner has not set forth any factual evidence from the specification or cogent scientific reasoning from the evidence in the specification as to what led him to judge that a solvates could not be formed and that person having ordinary skill in the art would have serious doubt that solvates of the inventive compounds could be formed without undue experimentation. The burden to provide such factual evidence is on the Examiner. *See In re Thrift* and *In re Lee, supra*. It is the Appellants' position that solvates of the claimed compounds can be formed using known techniques for making of solvates. The Examiner has not presented any evidence to dispute that a solvate could not be produced by exposing the compound to solvent and then isolating the solid.

The Examiner relies on *Morton International Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (Fed. Cir. 1993) to support his position that the only evidence necessary to make a *prima facie* case of non-enablement is that there are no working examples or guidance in the specification for forming solvates. The Morton case is not about producing solvates. The court in *Morton* did not make a finding that the claims were invalid for lack of enablement because there were no working examples, but because there was strong extrinsic evidence that working examples did not produce the claimed compound having "partial conductivity." The evidence was based on expert testimony and NMR analytical evidence and evidence that a person skilled in the art could not determine whether the examples formed compounds having the claimed "partial conductivity."

There is no *per se* rule that if the specification lacks working examples to form solvates,

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(2000). A copy of the definition is attached in APPENDIX B.

claims including solvates are not patentable for failure to comply with the enablement clause in the first paragraph of 35 U.S.C. § 112. It is not uncommon when claiming therapeutic compounds to claim the compound and also include pharmaceutical salts and solvates thereof. Such language can be found in numerous patents that do not specifically include working examples for forming solvates. See patents cited in APPENDIX D. See U.S. Patent No. 4,795,756 (abstract, claim 1, col. 3, line 20-24); U.S. Patent No. 6,100,271 (claim 1); U.S. Patent No. 6,103,730 (abstract, claim 1); U.S. Patent No. 6,316,444 (abstract, claim 1); U.S. Patent No. 6,335,324 (claim 1, col. 27, lines 61-67, 29, lines 51-55); and 6,376,472 (abstract, claim 1, col. 7, line 49 to col. 8, line 51)

This rejection under 35 U.S.C. § 112, first paragraph, fails because the Examiner has not presented any evidence to put into doubt that the formation of solvates of the compounds of the present invention by a person having ordinary skill in the art would require undue experimentation. See *In re Thrift, supra*. It is Appellants' position that a solvate of the inventive compounds can be made by using known techniques known to persons skilled in the art such as that outlined by the Examiner in his rejection.

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

REJECTION CLAIMS 19-25 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 19-25 stand rejected under 35 U.S.C. § 112, first paragraph, because the claims contain subject matter which is not described in the specification in such as way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner found that the term "cytokine" to be so broad that a person having ordinary skill in the art would have been required to engage in undue experimentation to determine what cytokine are within the scope of

the claims.

Base claim 19 is very clear and the Examiner understands the scope of the claim. As stated by the Examiner, the scope of the claim "is not the problem alleged." According to the Examiner, the "scope of the claim is clear: it covers any activity mediated by any cytokine" and that "[s]ince most cellular activities are mediated by cytokines, this in fact covers most biological activities of the cell." (paragraph bridging pages 13 and 14 of the Office Action, Paper No. 12).

Claim 19 is directed to a method of inhibiting an activity mediated by a cytokine. The method requires contacting cytokine responsive cells with a compound defined in claim 1 and then determining that the cellular process or activity mediated by the cytokine is inhibited. Any person skilled in the art would have understood the scope of the claim and that no undue experimentation would have been required. The Examiner has acknowledged the simplicity of the scope of the claim. However, the Examiner takes issue with the scope of the term "cytokines." This issue appears to forms the basis for his rejection.

In the rejection on pages 9 and 10, the Examiner has presented his own soliloquy on cytokines and how diverse they are in their structure and function. The Examiner has discussed chemokines, motogenic cytokines, B-cell growth factor, colony stimulating factors, angiogenesis factors, interlukins, and others. Nothing that the Examiner has presented is referenced to any documents of record in the application file. The burden is on the Examiner to support his argument with documentary evidence. *See In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002).

Claim 19 is not dependent on any particular type or kind of cytokine or what may be termed to be a cytokine. According to Stedmans, a cytokine is "[a]ny of numerous hormonelike, low-molecular-weight proteins, secreted by varous cell types, that regulate the intensity and

duration of immune response and mediate cell-cell communication ..." A copy of the definition from Stedman's is attached as APPENDIX C. In addition, the *Dictionary of Microbiology and Molecular Biology* defines "cytokine" as meaning "[i]n the human and animal body: a heterogeneous population of (glyco)proteins which form a dynamic network of intercellular messenger molecules that regulate various aspects of physiology, including the immune response to infection." A copy of the complete definition from the *Dictionary* is also attached as APPENDIX C.

The only function required in method claim 19 is that the cytokine mediate cell activity. No particular cytokine need be specified. It is a simple matter of contacting the cell with the compound as set forth in claim 1 and determining whether or not the cytokine activity is inhibited. The method recited in claim 19 is not so broad such that a person skilled in the art would not be able to practice the invention. According to a finding by the Examiner, all cytokines mediate cellular activity.

The Examiner argues that the method of claim 19 is not enabling because the scope of the compound is very large in that "[t]here are four variables each with a substantial number of choices for what these variables can be." While the Examiner maintains that claims 1 and 37 cover "billions of compounds," neither of these claims have been rejected as being non-enabling due to breadth of scope. In addition, claim 19-25 do not depend on claim 37.

The Examiner argues that the "invention is directed toward the action of cytokines and is therefore physiological in nature." The Examiner relies on *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and argues that it is "well established that 'the scope of enablement varies inversely with the degree of unpredictability of the factors involved,' and physiological activity is generally considered to be an unpredictable factor." Appellants do not disagree on this

point, however, the unpredictability of physiological activity of a cytokine is not at issue in the method recited base claim 19 or any claim dependent thereon. In applying the method of claim 19, it would have been known that a cell activity is mediated by a cytokine. The Examiner has conceded that all cytokines mediate cell activity. A person having ordinary skill in the art would have known what physiological activity involved. The method would require contacting the cell with a compound with a compound within the scope of claim 1 and then determining that the activity is inhibited by the compound. Therefore, the unpredictability is not a factor in determining whether undue experimentation would have been required to practice the method recited in the claim and the claims dependent thereon.

The Examiner considers the direction or guidance in the specification to be of "very limited value." The only evidence that the Examiner has put forth is that the specification discloses an "immense list of disorders" and a "dosage range" that "is as broad as a million fold range ... and is generic as to the particular disease." Contrary to the Examiner's position, the specification provides sufficient guidance and direction. The specification sets forth in detail by way of Example 11 a method of inhibiting Th1 differentiation in splenic cells *in vivo* by blocking IL-12 (a cytokine) signaling. Th1 or T1 differentiation was induced using IL-12. The cells were contacted with compounds from Examples 1, 2, 6 and 7, and then a determination is made that the Th1 or T1 differentiation was inhibited. The results are shown in Table 1 on page 60 of the specification. Accordingly, there is sufficient guidance by way of an example in the written description of the invention in the specification that would have enabled a person having ordinary skill in the art to practice the invention set forth in claims 19-25. The example is carried out *in vivo* (claim 20) and the cellular process is differentiation of naïve T cells (splenic T cells) into Th1 or T1 cells (claim 21). The example further discloses at page 60 of the specification

differentiation of naïve T cells to Th2 or T2 cells (claim 22). As for the activity defined in claims 23 and 24, the specification sets forth a number of examples of cytokines that are proinflammatory and antiinflammatory (see page 2, lines 5-19, page 2, line 28 to page 4, line 25 of the specification) as well as the cytokines that mediate, *inter alia*, cell differentiation as set forth in claim 25 (see page 2, lines 20-25).

The Examiner has not presented any evidence of record of the state of the art or the prior art. No patents or published literature articles are cited or used as references The Examiner's discussion of the state of the art is his own soliloquy. The Examiner has not met his burden of establishing the state of the art or prior art with evidence. *See In re Thrift* and *In re Lee, supra*. The method set forth in claims 19-25 is not rocket science. It is a simple matter of contacting a cell having an activity mediated by a cytokine with a compound within the scope of claim 1 and determining that the mediated activity is inhibited by the compound. A working example of the method is set forth in Example 11 in the specification. The level of skill required to practice the method is not beyond the level of skill of a person skilled in the art. The Examiner is asserting that cytokines are "extremely complex" and that they have "ubiquitous biological activities" which make the regulation of cytokines difficult. In the claimed method, the specific activity of the cytokine is immaterial. The claim is directed to a method the determines if the activity of the cytokine, whatever it is, is inhibited by a compound of claim 1. The method is not rocket science and would not entail undue experimentation to determine if the activity of the cytokine in question is inhibited.

The Examiner apparently is of the opinion that Examples 11 and 12 are not sufficient to support claims 19-25, however, no reasons are given. According to the Examiner, "Example 12 and both examples 11 show that most (but not all) of the compounds tested suppress IL-4 or IL-

12 signaling, or both" and that these "are just a tiny portion of the cytokines embraced, and these examples do not demonstrate that these compounds have any *in vivo* properties, as these are *in vitro* tests." There is no requirement that there be working examples for each class or category of cytokines to comply with the first paragraph requirement of 35 U.S.C. § 112. There is no requirement in 35 U.S.C. § 112 that the method recited in claims 19-25 be supported by examples that the compounds of claim 1 have *in vivo* properties. The examples in the specification provide sufficient guidance for a person having ordinary skill in the art to practice the method recited in claims 19-25.

The Examiner contends that the state of the art in the area of the invention "is low." According to the Examiner, most cytokines "are of unknown, or little known function" and that there is "no clear idea how many cytokines are there, as new ones are being discovered all the time." These are conclusory statements unsupported by evidence. See *In re Thrift* and *In re Lee, supra*. The argument by the Examiner is insufficient to establish the state of the art with respect to the method recited in claims 19-25, let alone establish that the state of the art "is low."

The Examiner further argues that "[e]xtensive experimentation will be needed" to practice the invention because of the complexity of the activity of cytokines. The Examiner presents a soliloquy on pages 14-19 regarding his characterization of cytokines. He cites the following web cites:

http://home.attbi.com/~bkrentzman/misc/how.things.work/dna.transcription/cytokines.html
http://www.copewithcytokines.de/cope.cgi?001668
http://www.psoriasis.org/enbrel.approval.jan02.htm
http://www.jnj.com/news_finance/402.htm
http://www.jnj.com/news/jnj news/20020329 0810.htm

The first four web cites were cited on the Examiner's PTO 692, but no copies were provided to Appellants. Copies of the contents of the web cites are attached in APPENDIX F. Note that a

search of the news article using the fourth web cite leads you to the fifth web site.

The Examiner uses an example, namely, adverse inhibiting effect of Remicade® and Enbrel on α-TNF activity as evidence that undue experimentation would be required to practice the method recited in claims 19-25. The relevance of this information to the amount of experimentation required to practice the method recited in claims 19-25 is not explained by the Examiner. The fact that suppression of one cytokine may have adverse effects or may mean that "another cytokine will take up the slack" does not establish that undue experimentation would be required to practice the method set forth in claims 19-25. The α-TNF promotes inflammation to fight infection. Therefore, the cytokine would come within the scope of claims 19, 20 and 23. The method is simple, cells responsive to the cytokine are contacted with a compound of claim 1, and then a determination is made if the cellular process or activity mediated by the cytokine is inhibited. The fact that the cytokine may produce an adverse effect if inhibited is not relevant and is not within the scope of the claimed subject matter. The fact that it is determined that a compound of claim 1 inhibits the activity of the cytokine is all that is necessary and that can be determined by merely observing if the expected activity is not present.

The Examiner cites MPEP Section 2164.01(a) that a conclusion of lack of enablement is based on evidence at the time the application was filed that would not have taught a person having ordinary skill in the art how to make and use the invention. There is no evidence in the record of this application that the information provided by the Examiner from the internet would have been known at the time the invention was made. For example, the information on Remicade® is from a Johnson and Johnson news article dated October 21, 2001 which is after the present application was filed (May 18, 2001). The information on Enbrel is dated January 16, 2002, which is again after the filing of the application. None of the other internet citations by the

Examiner are dated. Therefore, it is not possible to ascertain if the information contained therein was known at the time the present application was filed. Therefore, the Examiner's soliloquy on pages 14-19 of the Office action is not evidence of what was known to persons skilled in the art at the time the application was filed to establish the level of skill of the art. *See In re Thrift* and *In re Lee, supra.*

For the foregoing reasons, Appellants respectfully request that the Board reverse the Examiner.

CONCLUSION

In view of the foregoing arguments, Appellants submit that the Examiner has failed to establish a factual basis to support a conclusion that the present claimed subject matter fails to satisfy the requirements of 35 U.S.C. § 112, first and second paragraphs. It is respectfully submitted that the rejection of the claims on appeal is in error and that the rejections for obviousness be reversed.

To the extent necessary, a petition for an extension of time under 37 CFR 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

Date: June 9, 2003

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